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Chapter 36: Fungal Infections, Invasive

HISTOPLASMOSIS

- *Histoplasmosis* is primarily a pulmonary infection caused by inhalation of dust-borne microconidia of the dimorphic fungus *Histoplasma capsulatum*. Disseminated histoplasmosis may occur in those who are immunocompromised. In the United States, most disease is localized along the Ohio and Mississippi river valleys.

CLINICAL PRESENTATION AND DIAGNOSIS

- In the vast majority of patients, low-inoculum exposure to *H. capsulatum* results in mild or asymptomatic pulmonary histoplasmosis. The course of the disease is generally benign, and symptoms usually abate within a few weeks of onset. Patients exposed to a higher inoculum during a primary infection or reinfection may experience an acute, self-limited illness with flu-like pulmonary symptoms, including fever, chills, headache, myalgia, and nonproductive cough.
- Chronic pulmonary histoplasmosis generally presents as an opportunistic infection imposed on a preexisting structural abnormality, such as lesions resulting from emphysema. Patients demonstrate chronic pulmonary symptoms and apical lung lesions that progress with inflammation, calcified granulomas, and fibrosis. Progression of disease over a period of years, seen in 25%–30% of patients, is associated with cavitation, bronchopleural fistulas, extension to the other lung, pulmonary insufficiency, and often death.
- In patients exposed to a large inoculum and in immunocompromised hosts, progressive illness, disseminated histoplasmosis, may occur. The clinical severity of the diverse forms of disseminated histoplasmosis (**Table 36-1**) generally parallels the degree of macrophage parasitization observed.
- In most patients, serologic evidence (complement fixation test or immunodiffusion testing) remains the primary method in the diagnosis of histoplasmosis. Detection of histoplasma antigen by enzyme immunoassay in the urine, blood, or bronchoalveolar lavage fluid of infected patients provides rapid diagnostic information and is particularly useful in patients who are severely ill.

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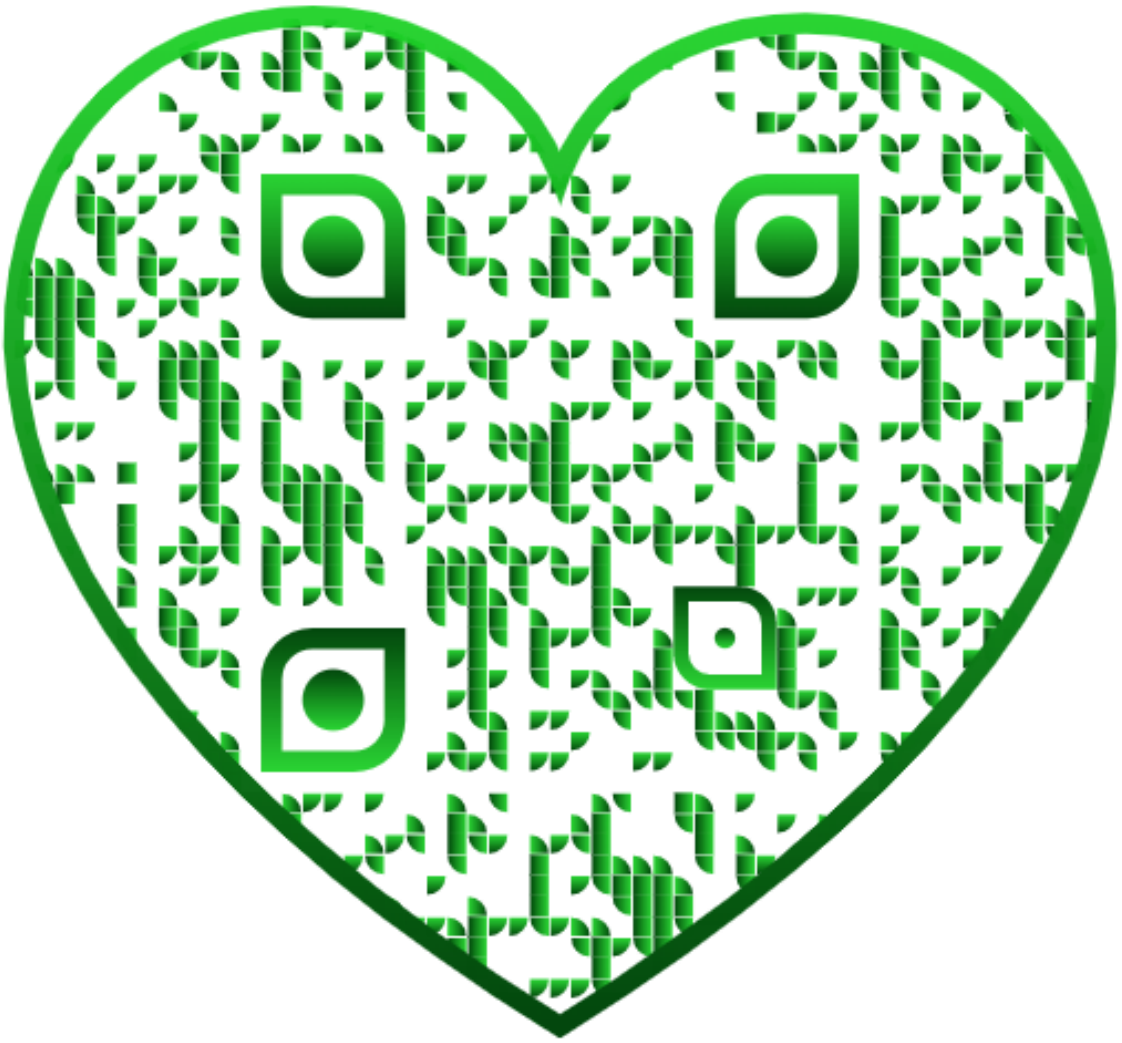

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TABLE 36-1

Clinical Manifestations and Therapy of Histoplasmosis

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Acute pulmonary histoplasmosis	
Asymptomatic or mild-to-moderate disease	*Asymptomatic, mild, or symptoms <4 weeks*: No therapy is generally required; itraconazole[a] orally (200 mg three times daily for 3 days and then 200 mg once or twice daily for 6–12 weeks) is recommended for patients who continue to have symptoms for greater than 1 month[a]
Moderately severe to severe diffuse pulmonary disease	Lipid amphotericin B 3–5 mg/kg/day IV for 1–2 weeks followed by itraconazole[a] orally 200 mg orally three times daily for 3 days, then twice daily for a total of 12 weeks of therapy; methylprednisolone (0.5–1 mg/kg daily IV) during the first 1–2 weeks of antifungal therapy is recommended for patients who develop respiratory complications, including hypoxemia or significant respiratory distress
CNS histoplasmosis	Amphotericin B should be used as initial therapy (lipid formulations at 5 mg/kg/day IV, for a total dosage of 175 mg/kg for 4–6 weeks, followed by itraconazole[a] orally 200 mg orally two or three times daily for at least a year; some patients may require lifelong therapy; response to therapy should be monitored by repeat lumbar punctures to assess *Histoplasma* antigen levels, WBC, and CSF antibody titers
Progressive histoplasmosis	*Moderately severe to severe*: Liposomal amphotericin B (3 mg/kg daily) IV, amphotericin B lipid complex (ABLC, 5 mg/kg daily) IV, or deoxycholate amphotericin B (0.7–1 mg/kg daily) for 1–2 weeks IV, followed by itraconazole[a] orally (200 mg orally twice daily for at least 12 months) *Mild to moderate*: Itraconazole[a] orally (200 mg orally twice daily for at least 12 months); immunosuppressed patients may require lifelong suppressive therapy with itraconazole[a] orally 200 mg daily

CNS, central nervous system; CSF, cerebrospinal fluid; IV, intravenous; WBC, white blood cell.

[a]Itraconazole plasma concentrations should be measured during the second week of therapy to ensure that detectable concentrations have been achieved. If the concentration is below 1 mcg/mL (mg/L; 1.4 µmol/L), the dose may be insufficient or drug interactions can be impairing absorption or accelerating metabolism, requiring a change in dosage. If plasma concentrations are greater than 10 mcg/mL (mg/L; 14 µmol/L), the dosage can be reduced.

TREATMENT

- Goals of Treatment: Resolution of clinical abnormalities, prevention of relapse, and eradication of infection whenever possible, although chronic suppression of infection can be adequate in immunosuppressed patients, including those with HIV disease.
- Recommended therapy for the treatment of histoplasmosis is summarized in **Table 36-1**.
- Response to therapy should be measured by resolution of radiologic, serologic, and microbiologic parameters and improvement in signs and symptoms of infection.

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- After the initial course of therapy for histoplasmosis is completed, lifelong suppressive therapy with oral azoles is recommended in some patients because of the frequent recurrence of infection.
- In regions experiencing high rates of histoplasmosis (>5 cases/100 patient-years), itraconazole 200 mg/day orally is recommended as prophylactic therapy in people with HIV.
- Relapse rates in AIDS patients not receiving preventive maintenance are 50%–90%.

BLASTOMYCOSIS

- North American *blastomycosis* is a systemic fungal infection caused by *Blastomyces dermatitidis.* Pulmonary disease can be acute or chronic and can mimic infection with tuberculosis, pyogenic bacteria, other fungi, or malignancy.
- Blastomycosis can disseminate to virtually every other body organ, and approximately 40% of patients with blastomycosis present with skin, bone and joint, or genitourinary tract involvement without any evidence of pulmonary disease.

CLINICAL PRESENTATION AND DIAGNOSIS

- Pulmonary blastomycosis is the most common manifestation and can range from asymptomatic infection to acute pneumonia, with or without respiratory failure, to chronic disease. Typical symptoms of acute pulmonary infection include fever, shaking chills, and a productive, purulent cough, with or without hemoptysis.
- Sporadic pulmonary blastomycosis may present as a more chronic or subacute disease, with low-grade fever, night sweats, weight loss, and a productive cough resembling that of tuberculosis rather than bacterial pneumonia. Chronic pulmonary blastomycosis is characterized by fever, malaise, weight loss, night sweats, chest pain, and productive cough.
- The simplest and most successful method of diagnosing blastomycosis is by direct microscopic visualization of the large, multinucleated yeast with single, broad-based buds in sputum or other respiratory specimens, following staining.

TREATMENT

- In the immunocompetent host, acute pulmonary blastomycosis can be mild and self-limited and may not require treatment. However, consideration should be given to treating all infected individuals to prevent extrapulmonary dissemination. All individuals with moderate-to-severe pneumonia, disseminated infection, or those who are immunocompromised require antifungal therapy (**Table 36-2**).
- In patients with mild-to-moderate pulmonary blastomycosis, itraconazole is effective; however, in patients with moderately severe to severe pulmonary disease, the clinical presentation of the patient, the immune competence of the patient, and the toxicity of the antifungal agents are the main determinants of the choice of antifungal therapy.
- In patients with mild-to-moderate pulmonary blastomycosis, **itraconazole** is effective; however, in patients with moderately severe to severe pulmonary disease, the clinical presentation of the patient, the immune competence of the patient, and the toxicity of the antifungal agents are the main determinants of the choice of antifungal therapy.
- All patients with disseminated blastomycosis, as well as those with extrapulmonary disease, require therapy.

TABLE 36-2

Therapy of Blastomycosis

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Type of Disease	Preferred Treatment
Pulmonary[a]	
Moderately severe to severe disease	Lipid formulation of amphotericin B 3–5 mg/kg IV daily or amphotericin B[b] 0.7–1 mg/kg IV daily (total dose 1.5–2.5 g) × 1–2 weeks or until improvement is noted, followed by itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily, × total of 6–12 months
Mild-to-moderate disease	Itraconazole[b,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily, for a total of 6 months[b]
CNS Disease	*Induction*: Lipid formulation of amphotericin B 5 mg/kg IV daily × 4–6 weeks, followed by an oral azole as consolidation therapy *Consolidation*: Voriconazole[d] 200–400 mg orally twice daily preferred. Alternatives include fluconazole 800 mg orally daily, or itraconazole[c] 200 mg two or three times daily orally, for ≥12 months and until resolution of CSF abnormalities
Disseminated or Extrapulmonary Disease	
Moderately severe to severe disease	Lipid formulation of amphotericin B 3–5 mg/kg IV daily or amphotericin B[b] 0.7–1 mg/kg IV daily × 1–2 weeks or until improvement is noted, followed by itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily × 6–12 months; treat osteoarticular disease with 12 months of antifungal therapy Most clinicians prefer to step-down to itraconazole[d] therapy once the patient's condition improves
Mild to moderate	Itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg once or twice daily × ≥12 months; treat osteoarticular disease with 12 months of antifungal therapy
Immunocompromised Host (Including Patients with AIDS, Transplants, or Receiving Chronic Glucocorticoid Therapy)	
Acute disease	Lipid formulation of amphotericin B 3–5 mg/kg IV daily or amphotericin B[a] 0.7–1 mg/kg IV daily × 1–2 weeks or until improvement is noted, then give suppressive therapy for a total of at least 12 months of therapy
Suppressive therapy	Itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily for a total of at least 12 months of therapy; lifelong suppressive therapy with oral itraconazole[d] 200 mg daily may be required for immunosuppressed patients in whom immunosuppression cannot be reversed and in patients who experience relapse despite appropriate therapy

CNS, central nervous system; CSF, cerebrospinal fluid; IV, intravenous.

[a]In the immunocompetent host, acute pulmonary blastomycosis can be mild and self-limited and may not require treatment.

[b]Deoxycholate amphotericin B.

[c]Serum levels of itraconazole should be determined after the patient has received itraconazole for ≥2 weeks to ensure adequate drug exposure.

[d]Azoles should not be used during pregnancy.

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COCCIDIOIDOMYCOSIS

- *Coccidioidomycosis* is caused by infection with *Coccidioides immitis* and *C. posadasii*. The endemic regions encompass the semiarid areas of the southwestern United States from California to Texas, known as the Lower Sonoran Zone.
- Factors for severe, disseminated infection include Filipino or African American race, pregnancy, male gender, neonates, and compromised cellular immune system (patients with AIDS or receiving corticosteroids, immunosuppressive agents, or chemotherapy).

CLINICAL PRESENTATION AND DIAGNOSIS

- Coccidioidomycosis encompasses a spectrum of illnesses, ranging from primary uncomplicated respiratory tract infection that resolves spontaneously to progressive pulmonary or disseminated infection.
- Approximately 60% of infected patients have an asymptomatic, self-limited infection without clinical or radiological manifestations. The remaining 40% of patients exhibit nonspecific symptoms that are often indistinguishable from ordinary upper respiratory infections, including fever, cough, headache, sore throat, myalgias, and fatigue that occur 1–3 weeks after exposure to the pathogen. A fine, diffuse rash may appear during the first few days of illness.
- Chronic, persistent pneumonia or persistent pulmonary coccidioidomycosis (primary disease lasting >6 weeks) is complicated by hemoptysis, pulmonary scarring, and the formation of cavities or bronchopleural fistulas.
- Disseminated infection occurs in less than 1% of infected patients. Dissemination may occur to the skin, lymph nodes, bone, meninges, spleen, liver, kidney, and adrenal gland. Central nervous system (CNS) infection occurs in ~16% of patients with disseminated infection.
- The diagnoses of coccidioidomycosis generally include identification or recovery of *Coccidioides* spp. from clinical specimens and detection of specific anticoccidioidal antibodies in serum or other body fluids.

TREATMENT

- Goals of Treatment: Desired outcomes of treatment are resolution of signs and symptoms of infection, reduction of serum concentrations of anticoccidioidal antibodies, and return of function of involved organs.
- Therapy of coccidioidomycosis is difficult, and the results are unpredictable. Patients with complicated disease or who are significantly immunocompromised should be treated.
- Azole antifungals, primarily fluconazole and itraconazole, are initially recommended therapy for most chronic pulmonary or disseminated infections.
- Amphotericin B is now usually reserved for patients with respiratory failure because of infection with *Coccidioides* spp., those with rapidly progressive coccidioidal infections, or women during pregnancy. Lipid formulations of amphotericin B have not been extensively studied for coccidioidomycosis but can offer a means of giving more drugs with less toxicity.
- Specific antifungals (and their usual dosages) for the treatment of coccidioidomycosis include IV lipid formulations of **amphotericin B** (3–5 mg/kg/day), IV or oral **fluconazole** (usually 400–800 mg/day, although dosages as high as 1200 mg/day have been used without complications), and **itraconazole** (200–300 mg orally twice daily or three times daily, as capsules or solution). If itraconazole is used, measurement of serum concentrations can be helpful to ascertain whether oral bioavailability is adequate.
- Therapy often ranges from 3–6 months to years in duration, and in some patients, lifelong suppressive therapy is needed to prevent relapses.
- Patients with disease outside the lungs should be treated with 400 mg/day of an oral azole. For meningeal disease, fluconazole 400 mg/day orally should be used; however, some clinicians initiate therapy with 800 or 1000 mg/day, and itraconazole doses of 400–600 mg/day are comparable.

CRYPTOCOCCOSIS

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- *Cryptococcosis* is a noncontagious, systemic mycotic infection caused by the ubiquitous encapsulated soil yeast *Cryptococcus neoformans*.

CLINICAL PRESENTATION AND DIAGNOSIS

- Primary cryptococcosis in humans almost always occurs in the lungs. Infection is acquired by inhalation of the organism.
- Disease may remain localized in the lungs or disseminate to other tissues, particularly the CNS, although the skin can also be affected.
- Symptomatic infections usually are manifested by cough, rales, and shortness of breath that generally resolve spontaneously. In the non-AIDS patient, the symptoms of cryptococcal meningitis are nonspecific. Headache, fever, nausea, vomiting, mental status changes, and neck stiffness are generally observed. In AIDS patients, fever and headache are common, but meningismus and photophobia are much less common than in non-AIDS patients.
- Examination of cerebrospinal fluid (CSF) in patients with cryptococcal meningitis generally reveals an elevated opening pressure, CSF pleocytosis (usually lymphocytes), leukocytosis, a decreased CSF glucose, an elevated CSF protein, and a positive cryptococcal antigen by latex agglutination.
- *C. neoformans* can be detected in ~60% of patients by India ink smear of CSF and cultured in more than 96% of patients.

TREATMENT

- The management of cryptococcosis includes systemic antifungal therapy, control of elevated intracranial pressure, and supportive care. Treatment of cryptococcosis is detailed in **Table 36-3**. For asymptomatic, immunocompetent persons with isolated pulmonary disease and no evidence of CNS disease, careful observation may be warranted.
- Most patients with mild-to-moderate pulmonary disease can be treated with fluconazole 400 mg daily for 6–12 months.
- Induction treatment with a combination of a liposomal amphotericin B (initial dose of 3 mg/kg/day) plus flucytosine (100 mg/kg/day) is recommended for initial therapy in all patient groups. Lipid formulations of amphotericin B are preferred. A minimum of 2 weeks of treatment is recommended for HIV-coinfected and organ transplant recipients and 4–6 weeks (or 2 weeks after CSF sterility) for previously healthy patients.
- After induction, consolidation therapy with fluconazole (400–800 mg/day) for 8 weeks is recommended in all patient groups. Maintenance therapy with a lower dose of fluconazole (200 mg/day) for at least 6–12 months is subsequently recommended.

TABLE 36-3

Therapy of Cryptococcosis[a,b]

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Non-immunocompromised Patients (Non–HIV-Infected, Nontransplant)	
Meningoencephalitis *without* neurological complications, in patients in whom CSF yeast cultures are negative after 2 weeks of therapy	*Induction*: Amphotericin B[c,d] IV 0.7–1 mg/kg/day *plus* flucytosine 100 mg/kg/day orally in four divided doses × ≥4 weeks
Meningoencephalitis with neurological complications	*Induction*: Same as for patients without neurologic complications, but consider extending the induction therapy for a total of 6 weeks.
Follow all regimens with suppressive therapy	*Consolidation*: Fluconazole 400–800 mg orally daily × 8 weeks *Maintenance*: Fluconazole 200 mg orally daily × 6–12 months
Mild-to-moderate pulmonary disease (nonmeningeal	Fluconazole 400 mg orally daily × 6–12 months

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disease)	
Severe pulmonary cryptococcosis	*Same as CNS disease × 12 months*
Cryptococcemia (nonmeningeal, nonpulmonary disease)	*Same as CNS disease × 12 months*
HIV-Infected Patients	
Primary therapy; induction and consolidation[e]	*Preferred regimen*: *Induction*: Amphotericin B[c,d] IV 0.7–1 mg/kg IV daily *plus* flucytosine 100 mg/kg/day orally in four divided doses for ≥2 weeks. Alternative regimens, in order of preference: Amphotericin B[c,e] IV 0.7–1 mg/kg IV daily × 4–6 weeks *or* liposomal amphotericin B 3–4 mg/kg IV daily[f] × 4–6 weeks *or* ABLC 5 mg/kg IV daily × 4–6 weeks *or* amphotericin B[c] IV 0.7 mg/kg IV daily, *plus* fluconazole 800 mg (12 mg/kg) orally daily × 2 weeks, followed by fluconazole 800 mg (12 mg/kg) orally daily × ≥8 weeks *or* fluconazole ≥800 mg (1200 mg/day is preferred) orally daily *plus* flucytosine 100 mg/kg/day orally in four divided doses × 6 weeks *or* Fluconazole 800–1200 mg/day orally daily × 10–12 weeks (a dosage ≥1200 mg/day is preferred when fluconazole is used alone)[g]
Follow all regimens with suppressive therapy	*Consolidation*: Fluconazole 400 mg (6 mg/kg) orally daily × ≥8 weeks *Maintenance*: Fluconazole 200 mg orally daily × ≥1 year[h,i]
Organ Transplant Recipients	
Mild-to-moderate non-CNS disease or mild-to-moderate symptoms without diffuse pulmonary infiltrates	Fluconazole 400 mg (6 mg/kg) orally daily × 6–12 months
CNS disease, moderately severe or severe CNS disease or disseminated disease without CNS disease, or severe pulmonary disease without evidence of extrapulmonary or disseminated disease	*Induction*: Liposomal amphotericin B 3–4 mg/kg IV daily,[f] or ABLC 5 mg/kg IV daily *plus* flucytosine 100 mg/kg/day orally in four divided doses × ≥2 weeks If induction therapy does not include flucytosine, consider a lipid formulation of amphotericin B for ≥4–6 weeks of induction therapy. Consider the use of a lipid formulation of amphotericin B lipid formulation (6 mg/kg IV daily) in patients with a high-fungal burden disease or relapse of disease *Consolidation*: Fluconazole 400–800 mg (6–12 mg/kg) per day orally for 8 weeks *Maintenance*: Fluconazole 200–400 mg per day orally for 6–12 months
Follow all regimens with suppressive therapy	*Consolidation*: Fluconazole 400–800 mg (6–12 mg/kg) per day orally for 8 weeks *Maintenance*: Fluconazole 200–400 mg per day orally for 6–12 months

ABLC, amphotericin B lipid complex; CNS, central nervous system; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IV, intravenous.

[a]When more than one therapy is listed, they are listed in order of preference.

[b]See Chapter 144, "Invasive Fungal Infections," *DiPiro's Pharmacotherapy: A Pathophysiologic Approach,* 12th ed., for definitions of induction, consolidation, suppressive/maintenance therapy, and prophylactic therapy.

[c]Deoxycholate amphotericin B.

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[d]In patients with or at risk of renal disease, lipid formulations of amphotericin B can be substituted for deoxycholate amphotericin B. Doses are liposomal amphotericin B 3–4 mg/kg IV daily or ABLC 5 mg/kg IV daily.

[e]Initiate highly active antiretroviral therapy (HAART) therapy 2–10 weeks after commencement of initial antifungal treatment.

[f]Liposomal amphotericin B has been given safely up to 6 mg/kg daily; could be considered in treatment failure or in patients with a high fungal burden.

[g]Or until CSF cultures are negative.

[h]Consider discontinuing suppressive therapy during HAART in patients with a CD4 cell count ≥100 cells/μL (0.1×10^9/L) and an undetectable or very low HIV RNA level sustained for ≥3 months (with a minimum of 12 months of antifungal therapy). Consider reinstitution of maintenance therapy if the CD4 cell count decreases to <100 cells/μL (0.1×10^9/L).

[i]Drug level monitoring is strongly advised.

CANDIDA INFECTIONS

- Eight species of *Candida* are regarded as clinically important pathogens in human disease: *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. stellatoidea*, *C. guilliermondii*, *C. lusitaniae*, and *C. glabrata*. *C. albicans* is a normal commensal of the skin, female genital tract, and entire gastrointestinal (GI) tract of humans.
- Candidiasis can cause mucocutaneous or systemic infection, including endocarditis, peritonitis, arthritis, and infection of the CNS.

HEMATOGENOUS CANDIDIASIS

- Dissemination of *C. albicans* can result in infection in single or multiple organs, particularly the kidney, brain, myocardium, skin, eye, bone, and joints.
- *Candida* is generally acquired via the GI tract, although organisms may also enter the bloodstream via indwelling IV catheters.
- Major risk factors for hematogenous candidiasis include neutropenia, the use of central venous catheters, total parenteral nutrition, receipt of multiple antibiotics, extensive surgery and burns, renal failure and hemodialysis, mechanical ventilation, and prior fungal colonization.
- Several rapid diagnostic methods are available to identify candida pathogens including matrix-assisted laser desorption/ionization time-of-flight intact cell mass spectrometry, a multiplex polymerase chain reaction, and T2 magnetic resonance assays.
- Treatment of candidiasis is presented in **Table 36-4**.

TABLE 36-4

Antifungal Therapy of Invasive Candidiasis

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Prophylaxis of Candidemia	
Non-neutropenic patients	Not recommended except for severely ill/high-risk patients in whom fluconazole IV/oral 400 mg daily should be used (see Chapter 144, "Invasive Fungal Infections," *DiPiro's Pharmacotherapy: A Pathophysiologic Approach,* 12th ed.)
Neutropenic patients[a]	Fluconazole IV/oral 400 mg daily *or* itraconazole solution 2.5 mg/kg every 12 hours orally *or* micafungin 50 mg (1 mg/kg

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	in patients under 50 kg) IV daily; the optimal duration of therapy is unclear but at a minimum should include the period at risk for neutropenia
Solid-organ transplantation, liver transplantation	*Patients with key risk factors*[b]: Fluconazole 400 mg orally daily is preferred
Empirical (Preemptive) Antifungal Therapy	
Suspected disseminated candidiasis in febrile non-neutropenic patients	None recommended; data are lacking defining subsets of patients who are appropriate for therapy (see Chapter 144, "Invasive Fungal Infections," *DiPiro's Pharmacotherapy: A Pathophysiologic Approach,* 12th ed.)
Suspected candidiasis in febrile neutropenic patients	A lipid formulation of amphotericin B, caspofungin, micafungin, voriconazole, isavuconazole, posaconazole, or itraconazole for duration of neutropenia
Initial Antifungal Therapy of Documented Candidemia and Acute Hematogenously Disseminated Candidiasis, Unknown Species	
Patients who are less critically ill and who have had no recent azole exposure	*Remove existing central venous catheters when feasible plus fluconazole IV (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) or an echinocandin;* treatment duration: 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection
Patients with recent azole exposure, moderately severe or severe illness, or who are at high risk of infection due to *C. glabrata* or *C. krusei*	An echinocandin Transition from an echinocandin to fluconazole IV/oral is recommended for patients who are clinically stable and have isolates (eg, *C. albicans*) likely to be susceptible to fluconazole
Antifungal Therapy of Specific Pathogens	
C. albicans, C. tropicalis, and *C. parapsilosis*	Fluconazole IV/oral 6 mg/kg/day *or* an echinocandin; transition to fluconazole is recommended in patients who are clinically stable and whose isolates are likely to be susceptible to fluconazole (eg, *C. albicans*); voriconazole IV (400 mg [6 mg/kg] twice daily × two doses then 200 mg [3 mg/kg] twice daily thereafter) is efficacious, but offers little advantage over fluconazole; it may be utilized as step-down oral therapy for selected cases of candidiasis due to *C. krusei* or voriconazole-susceptible *C. glabrata* *Patients intolerant or refractory to other therapy*: Amphotericin B lipid complex IV 3–5 mg/kg/day Liposomal amphotericin B IV 3–5 mg/kg/day
C. krusei	An echinocandin[c]
C. lusitaniae	Fluconazole IV/orally 6 mg/kg/day
C. glabrata	An echinocandin[c] (transition to fluconazole or voriconazole therapy is not recommended without confirmation of isolate susceptibility)
Urinary candidiasis	*Asymptomatic disease*: Generally no therapy is required *Symptomatic or high-risk patients*[d]: Removal of urinary tract instruments, stents, and Foley catheters, +7–14 days therapy with fluconazole 200 mg orally daily *or* amphotericin B IV 0.3–1 mg/kg/day

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IV, intravenous.

[a]Patients at significant risk for invasive candidiasis include those receiving standard chemotherapy for acute myelogenous leukemia, allogeneic bone marrow transplants, or high-risk autologous bone marrow transplants. However, among these populations, chemotherapy or bone marrow transplant protocols do not all produce equivalent risk, and local experience should be used to determine the relevance of prophylaxis.

[b]Risk factors include re-transplantation, re-operation, renal failure requiring hemodialysis, transfusion of ≥40 units of cellular blood products, including platelets, packed red blood cells, and auto transfusion, choledochojejunostomy, and *Candida* colonization in the perioperative period.

[c]Echinocandin = caspofungin 70 mg loading dose, then 50 mg IV daily maintenance dose, or micafungin 100 mg daily, or anidulafungin 200 mg loading dose, then 100 mg daily maintenance dose.

[d]Patients at high risk for dissemination include neutropenic patients, low-birth-weight infants, and patients who will undergo urologic manipulation.

ASPERGILLUS INFECTIONS

- *Aspergillus fumigatus* is the most commonly observed pathogen, followed by *A. flavus.*
- Invasive aspergillosis commonly affects immunocompromised patients and patients with acute myeloid leukemia and those who undergo allogeneic hematopoietic stem cell transplantation who develop graft-versus-host disease are at highest risk. Aspergillosis is generally acquired by inhalation of airborne conidia that are small enough (2.5–3 mm) to reach the alveoli or the paranasal sinuses.
- Superficial or locally invasive infections of the ear, skin, or appendages can often be managed with topical antifungal therapy.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

- Allergic manifestations of *Aspergillus* range in severity from mild asthma to allergic bronchopulmonary aspergillosis characterized by severe asthma with wheezing, fever, malaise, weight loss, chest pain, and a cough productive of blood-streaked sputum.
- Therapy is aimed at minimizing the quantity of antigenic material released in the tracheobronchial tree.
- Antifungal therapy is controversial in the management of allergic manifestations of aspergillosis, although some patients have demonstrated a decrease in their glucocorticoid dose following therapy with itraconazole.

INVASIVE ASPERGILLOSIS

- Patients with invasive aspergillosis generally have blunted or nonspecific signs and symptoms of infection due to impaired inflammatory responses. Patients often present with classic signs and symptoms of acute pulmonary embolus: pleuritic chest pain, fever, hemoptysis, and friction rubs.
- Demonstration of *Aspergillus* by repeated culture and microscopic examination of tissue provides the most firm diagnosis.

TREATMENT

- **Voriconazole** is the drug of choice for primary therapy of most patients with invasive aspergillosis as it provided improved survival and fewer side effects. Alternative agents include **isavuconazole** and **posaconazole.**
- Combination therapies such as voriconazole and an echinocandin or amphotericin B and caspofungin have shown some benefits but further studies are needed.
- **Caspofungin** is indicated for treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies such as amphotericin B; however, response rates are lower.

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See Chapter 149, Invasive Fungal Infections, authored by Peggy L. Carver and Gregory A. Eschenauer, for a more detailed discussion of this topic.

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